# Commentary
# Immunosedation: a consideration for sepsis
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## Abstract

In a recent issue of *Critical Care*, Qiao and colleagues showed in a rat model of sepsis that dexmedetomidine and midazolam suppress the generation of pro-inflammatory mediators but the effects vary between agents. While dexmedetomidine limited apoptosis to a greater extent than midazolam, both agents significantly reduced short-term mortality compared with saline. This study, in addition to those by others, suggests there are disparate immunomodulating effects between sedatives. Clinical studies are warranted to investigate whether these effects impact outcomes of septic patients. Perhaps one day the choice of sedative in septic patients will not be based solely on sedative properties but rather immunosedative profiles.

In a recent issue of *Critical Care*, Qiao and colleagues [1] used a cecal ligation model of sepsis to compare the immunomodulating effects of dexmedetomidine, midazolam, and saline (placebo). They demonstrated that, over the course of an 8-hour infusion period, both sedatives significantly reduced the production of tumor necrosis factor-alpha (TNF-$\alpha$) but that only dexmedetomidine decreased interleukin (IL)-6 generation. Similarly, dexmedetomidine limited the splenic expression of caspase 3, a marker of apoptosis, to a greater extent than midazolam when compared with placebo. Mortality rates at 24 hours were similar between sedatives and were significantly reduced compared with placebo.

*In vitro* and other animal studies of sepsis have shown that dexmedetomidine suppresses the expression of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), TNF-$\alpha$, IL-1$\beta$, IL-6, and interferon-gamma (IFN-$\gamma$) [2-4]. These effects appear to be dose-dependent across the range of commonly used doses and time-dependent in that greater anti-inflammatory effects are observed if dexmedetomidine is started earlier after the exposure of endotoxin [3-5]. Reversal of these effects occurs when alpha-2 antagonists are concomitantly administered with dexmedetomidine, suggest-

ing that neural-immune modulation involving alpha-2 stimulation is essential to the anti-inflammatory mechanism of dexmedetomidine [2]. Of note, iNOS expression is enhanced at supratherapeutic concentrations of dexmedetomidine and further suggests that alpha-2 selectivity contributes to the anti-inflammatory action of dexmedetomidine [2]. Perhaps most intriguing is that hemodynamic stability and short-term survival rate emulate the dose-dependent and time-dependent anti-inflammatory effects of dexmedetomidine in these animal models of sepsis [3-5].

Benzodiazepines have also demonstrated dose-dependent suppression of COX-2, iNOS, and pro-inflammatory mediators in models of sepsis [6-10]. These studies suggest that the mechanism is mediated by inhibiting nuclear translocation of nuclear factor-kappa-B, reducing phosphorylation of p38 mitogen-activated protein, and stabilizing mast cells. The results of animal studies have shown conflicting outcomes with benzodiazepines, in contrast to dexmedetomidine, as survival rate is lower and organ function unaffected but bactericidal effect enhanced with benzodiazepine therapy [10].

Few studies have investigated the immunomodulating effects of sedatives in critically ill patients. In surgical patients, dexmedetomidine 0.2 to 2.5 $\mu$g/kg per hour reduced IL-6 over the course of an 8-hour period to a greater extent than propofol 1 to 3 mg/kg per hour [11]. Also in surgical patients, midazolam 0.02 to 0.06 mg/kg per hour reduced TNF-$\alpha$, IL-1$\beta$, and IFN-$\gamma$ after 48 hours whereas propofol 0.5 to 1.5 mg/kg per hour increased the production of these pro-inflammatory cytokines [12]. A direct comparison of dexmedetomidine 0.2 to 2.5 $\mu$g/kg per hour and midazolam 0.1 to 0.5 mg/kg per hour in septic patients showed that only dexmedetomidine suppressed the expression of TNF-$\alpha$, IL-1$\beta$, and IL-6; however, both agents improved oxygenation

COX-2 = cyclooxygenase-2; IFN-$\gamma$ = interferon-gamma; IL = interleukin; iNOS = inducible nitric oxide synthase; TNF-$\alpha$ = tumor necrosis factor-alpha.

as assessed by gastric mucosal pH [13]. In a subgroup of 39 septic patients from the MENDS (maximizing efficacy of targeted sedation and reducing neurological dysfunction) trial, the risk of dying was lower in the group that received dexmedetomidine compared with lorazepam (hazard ratio = 0.3, 95% confidence interval = 0.1 to 0.9, $P = 0.036$) [14]. The SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) study compared dexmedeto-midine and midazolam and reported a lower overall infection rate in the dexmedetomidine group (10.2% versus 19.7%, $P = 0.02$), but this may be attributed to a shorter ventilator requirement in this group rather than different immunomodulating properties of the sedatives [15]. Mortality rates at day 30 were similar between groups.

Should a particular class of sedative be preferred when sedating the septic patient? At present, the answer to this question is 'no' or at least 'not yet'. What is evident is that sedatives have immunomodulating properties and that auto-nomic activity influences cytokine expression. Indeed, adrener-gic catecholamines are known to influence immune responses and the process of inflammation [16]. Animal models of sedatives in sepsis rarely administered vasopressors for hemodynamic support, but it is conceivable that a particular vasopressor-sedative combination may be preferentially chosen to counterbalance their immunomodulating effects or enhance a specific effect. Septic patients frequently receive other immunomodulating therapies, including corticosteroids, drotrecogin, opioid analgesics, propofol, or immunonutrients [17,18]. How these agents interact with alpha-2 agonists or benzodiazepines is unknown, but presumably the use of these modalities was distributed equally in the few clinical studies conducted to date. Hypotension is a particular concern of using an alpha-2 agonist in sepsis. Data from animal studies, however, demonstrate improved hemodynamic profiles as the pro-inflammatory process subsides with dexmedetomidine administration [3-5].

Whether sedatives possess dose-dependent immunomodulat-ing effects has not been studied in critically ill patients. Animal data, however, suggest that dexmedetomidine may possess an optimal dose for its immunomodulating activity [3-5]. This dose would likely vary between patients and within the same patient over time. The logical question if such a dose does exist is what to do if additional sedation is required. Or is this, in addition to shorter ventilator requirements and improved neurologic recovery, justification for minimizing sedation? Another intriguing observation is the time-dependent immuno-modulating effect of dexmedetomidine because, in theory, dexmedetomidine may be an ideal sedative to initiate in early sepsis but other sedatives may be preferred later [3-5]. Does this necessitate changing the sedative agent as the sepsis process progresses? This is not unlike the scenario of the patient perceived to be unresponsive to a particular antibiotic who is changed to another class of antibiotic for greater response. Obviously, these queries are speculative. The

studies conducted to date in animal models of sepsis show that there are disparate immunomodulating effects and possibly therapeutic outcomes between sedatives [1-17]. Perhaps one day the choice of sedative in septic patients will not be based solely on sedative properties but rather immunosedative profiles.

## Competing interests

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